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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,943	11/09/2006	Soo-Hyun Kim	UTCA-13144	2208

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MEDLEN & CARROLL, LLP
101 HOWARD STREET
SUITE 350
SAN FRANCISCO, CA 94105

EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,943	KIM ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/07/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-10) and of the Seq. Id. No.: 3 as elected specie, in the reply filed on 03/07/2008 is acknowledged.

Status of the claims

2. In the amendment filed on 03/07/2008, Applicants amended claims 1and 5-9, and cancelled claims 3-4, and 11-44. The claims are 1-2 and 5-10 are pending and are being examined.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the independent claim 1 is drawn to a genus of nucleic acids comprising a sequence at least 80% identical to SEQ ID NO: 15, wherein said sequence encodes IL-32, and wherein said sequence comprises: a)

exon 3 in substantially contiguous association with exon 4, and b) exon 7 in substantially contiguous association with exon 8.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure (not even the whole DNA sequence encoding the claimed polypeptide product) in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved to retain the function of the genus of proteins named IL-32. There is no description of the IL-32 per se that the nucleic acid is supposed to encode for. The specification, describes IL-32 in paragraphs [0041] as "interleukine-32," "IL-32," "TAIF," "tumor necrosis factor-alpha inducing factor," "NK4," and "natural killer cell transcript 4," or human IL-32 gene (e.g., Homo sapiens--SEQ ID NO: 11), and its gene products (e.g., wild type alpha, beta, gamma and delta isoforms, and variants thereof). IL-32 variants that differ from the wild type IL-32 sequences in fewer than 20% of the residues (preferably 10% or fewer, more preferably 5% or fewer and most preferably 1% or fewer), are also suitable for use in the methods and compositions of the present invention (this includes but is not limited to the gene product corresponding to the murine cDNA fragment disclosed as SEQ ID NO: 12). In other embodiments of the present invention, alleles of IL-32 that result from a

mutation that generally produce altered mRNAs or polypeptides whose *structure or function may or may not be altered*. Any given gene may have none, one or many allelic forms. Common mutational changes that give rise to alleles are generally ascribed to deletions, additions or substitutions of nucleic acids. Each of these types of changes may occur alone, or in combination with the others, and at the rate of one or more times in a given sequence [0083]. Still other embodiments provide mutant or variant forms of IL-32. It is possible to modify the structure of a peptide having an activity of IL-32 for such purposes as enhancing therapeutic or prophylactic efficacy, or stability (e.g., ex vivo shelf life, and/or resistance to proteolytic degradation in vivo). Such modified peptides are considered functional equivalents of peptides having an activity of the subject IL-32 proteins as defined herein. A modified peptide can be produced in which the amino acid sequence has been altered, such as by amino acid substitution, deletion, or addition. In some embodiments, preferred IL-32 variants include IL-32 agonists (e.g., IL-32 variants that possess TNF-α inducing activity), while other preferred IL-32 variants include IL-32 antagonists (e.g., IL-32 variants that do not possess TNF-α inducing activity and that inhibit the TNF-α inducing activity of wild type IL-32 proteins) [0104]. Given at least three categories of definitions for "IL-32", a person of ordinary skill in the art would not be able to envision the exact nucleic clamed since there is no clear guidance from the specification. The disclosure would be considered adequate if, for instance, the nucleic acid claimed would *consist* of nucleic acids designated by their Seq. Id. Nos. , as for example Seq. Id. No.3.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polynucleotide species (SEQ ID NO: 3) and one polypeptide species (SEQ ID NO: 7) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments and with at least 80%, 90% and 95%, 99% sequence identity to a nucleic acid comprising the sequence of SEQ ID NO: 15.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid consisting of the sequence of SEQ ID NO: 3 or an isolated nucleic acid molecule encoding the polypeptide of SEQ ID NO: 7, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

5. Claims 1-2 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid consisting of the sequence of SEQ ID NO: 3 or an isolated nucleic acid molecule encoding the polypeptide of SEQ ID NO: 7, does not reasonably provide enablement for an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments and with at least 80%, 90% and 95%, 99% sequence identity to a nucleic acid comprising the sequence of SEQ ID NO: 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are drawn to a genus of nucleic acids comprising a sequence at least 80% identical to SEQ ID NO: 15, wherein said sequence encodes IL-32, and wherein said

sequence comprises: a) exon 3 in substantially contiguous association with exon 4, and b) exon 7 in substantially contiguous association with exon 8.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The invention comprises a new cytokine, IL-32 which is defined by Applicant in paragraphs [0041] as "interleukine-32," "IL-32," "TAIF," "tumor necrosis factor-alpha inducing factor," "NK4," and "natural killer cell transcript 4," or human IL-32 gene (e.g., Homo sapiens--SEQ ID NO: 11), and its gene products (e.g., wild type alpha, beta, gamma and delta isoforms, and variants thereof). IL-32 variants that differ from the wild type IL-32 sequences in fewer than 20% of the residues (preferably 10% or fewer, more preferably 5% or fewer and most preferably 1% or fewer), are also suitable for use in the methods and compositions of the present invention (this includes but is not limited to the gene product corresponding to the murine cDNA fragment disclosed as SEQ ID NO: 12). In other embodiments of the present invention, alleles of IL-32 that result from a mutation that generally produce altered mRNAs or polypeptides whose *structure or function may or may not be altered*. In the prior art, the nucleic acid sequence encoding

the IL-32 of Seq. Id. No. 7 was known. However, Applicant claims a whole genus based on unnamed mutations of the Seq. Id. No.7, with undisclosed alleles of IL 32 without disclosing their functionality and not even their structure.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional

configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133).

However, except for the IL-32 of Seq. Id. No. 7, there are no methods or working examples disclosed in the instant application whereby the variants of the IL-32 claimed have any functionality which is linked to their structure. The unpredictability of the art is *very high* with regards to making functional mutants with unspecified structural mutations.

Therefore, undue experimentation would be required of the skilled artisan to introduce and express unspecified structural variants of the polynucleotide of Seq. Id. No.: 3 into the cell of an organism and have them express functional proteins.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional

limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1,2 and 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Since the claims are not properly described, the metes and bounds of the claims cannot be determined.

Also, the independent claim 1 recite that the claimed nucleic acid comprises: “exon 3 in substantially contiguous association with exon 4, and b) exon 7 in substantially contiguous association with exon 8.” The phrase “substantially contiguous” renders the claim indefinite because it is no clear what exactly is encompassed by it. For instance one cannot determine if there are any intervening sequences in between the exons, if the exons are part of the same reading frame or if there are any nucleotides added or deleted in each exon.

The claim 2 is indefinite because is drawn to a nucleic acid encoding "an" alpha isoform of IL-32 and it is not clear if there are multiple alpha isoform or if "the” alpha isoform of Seq. Id. No.: 7 was the intended meaning.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 5-6 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (WO/02/059260, 0801/2002- cited by Applicant).

Tang et al. teach the Seq. Id. No.: 118 which contains a fragment between base pairs 100-207 which is 99.1% identical with the Seq. Id. No.: 15 claimed in the instant Application. Tang et al. also teach recombinant constructs comprising a nucleic acid having a fragment of Seq. Id. No.: 118. The recombinant construct may comprise a vector having the fragment inserted. the vector may further comprise regulatory sequences, including for example, a promoter, operably linked to the open reading frame "Operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence ((p.20, lines 11-33).

Therefore, Tang et al. anticipated all the limitations of the claims 1, 5-6 and 8-10.

10. Claims 1-2 and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by National Institutes of Health, Mammalian Gene Collection (MGC) entry: AGENCOURT_10614895 NIH_MGC_127 Homo sapiens cDNA clone IMAGE: 6745305

available 10/18/2002 (GenBank Accession: BU963861, See also result #1 from the score search for Seq. Id. No.:7 in the EST database-Search Result 20080519_112916_us-10-578-943-7.rst).

The sequence contains an open reading frame which translated from nucleotide 104, would encode the full length of the IL-32 alpha of Seq. Id. No.:7. Thus the sequence would intrinsically contain all the limitations of claims 1-2 and 5-6. The only difference between the BU963861sequence and the Seq. Id. No.: 3 of the instant Application, which also encoded the protein of Seq. Id. No.:7 is that the BU963861 sequence contains a silent mutation at nucleotide 166 (a "C") (codon GC**C** which encodes for an Alanine). The corresponding position in Seq. Id. No.: 3 is nucleotide 63 (a "T") (codon GC**T** which encodes an Alanine too). Thus, the BU963861 sequence encodes the protein of Seq. Id. No. 7 without being 100% identical with the Seq. Id. No.:3

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 8-10 rejected under 35 U.S.C. 103(a) as being unpatentable over National Institutes of Health, Mammalian Gene Collection (MGC) entry: AGENCOURT_10614895 NIH_MGC_127 Homo sapiens cDNA clone IMAGE: 6745305 in view of Sibson et al. (WO/94/01548).

15. The claims are drawn to a nucleic acid comprising a sequence at least 80% identical to SEQ ID NO: 15, wherein said sequence encodes IL-32, and wherein said sequence comprises: a) exon 3 in substantially contiguous association with exon 4, and b) exon 7 in substantially contiguous association with exon 8. The sequence is operably linked to a heterologous promoter which is comprised within a vector which can be hosted in a cell.

The considerations regarding the Sequence with GenBank Accession: BU963861 were presented supra. There is no express teaching with regard to expressing the open reading frame operably linked to a promoter that is part of an expression vector that is hosted in a cell.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA's disclosed by the primary reference(s) to express and then isolate the encoded polypeptide as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Drmanac et al., U.S.Pub. No. 20030073623;

Bejanin et al., WO/02/094864, 11/28/2002;

Bejanin et al. WO/02/083898, 10/24/2002.

They all disclose sequences that are more than 95% identical with the claimed Seq. Id. No.: 15.

Conclusion

17. SEQ ID NO: 3 is free of the prior art.

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/ Ph.D.

Primary Examiner, Art Unit 1647